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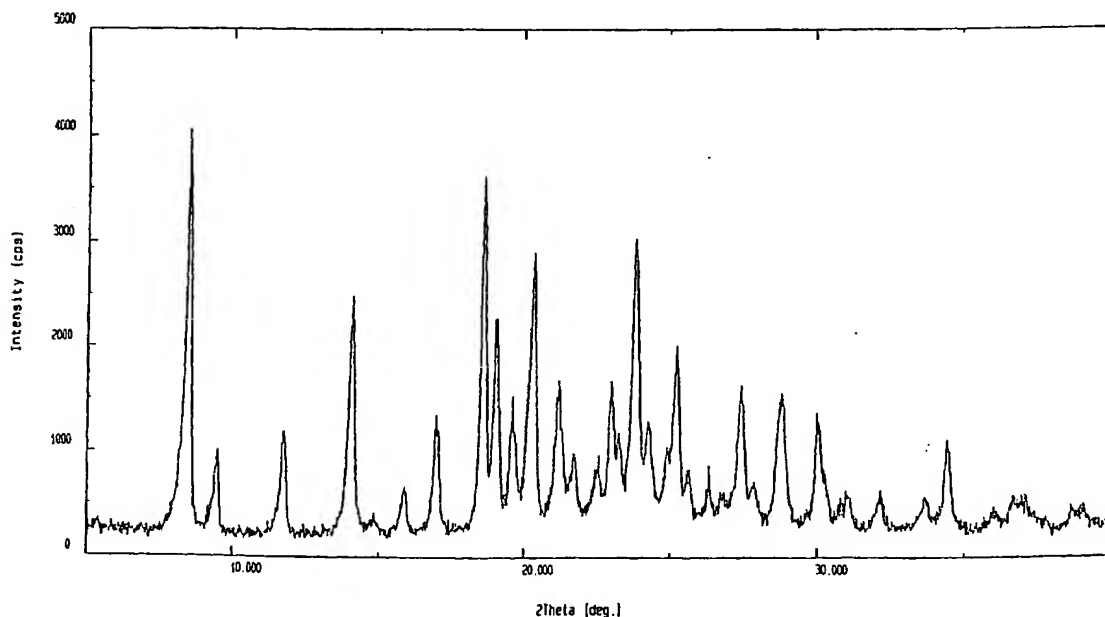
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(54) Title: **CRYSTALLINE ACID SALTS OF CEFDINIR AND PROCESS FOR PREPARING CEFDINIR USING SAME**



(57) Abstract: High purity cefdinir is prepared in a high yield by a process comprising the steps of: treating a cefdinir intermediate with a formic acid-sulfuric acid mixture or a formic acid-methanesulfonic acid mixture to obtain a crystalline salt of cefdinir and reacting the crystalline salt with a base in a solvent.

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CRYSTALLINE ACID SALTS OF CEFDINIR AND PROCESS FOR PREPARING CEFDINIR USING SAME

Field of the Invention

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The present invention relates to crystalline acid salts of cefdinir, a process for their preparation and a process for preparing cefdinir using the salts.

Background of the Invention

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In the preparation of cefdinir, a cephalosporin antibiotic, deprotection reaction of the carboxy-protected cefdinir is usually conducted in a strongly acidic medium, e.g., trifluoroacetic acid (US Patent No. 4,559,334). Such a strong acid treatment step, however, generates undesired by-products including E-isomer (anti-form) of cefdinir; and, as a result, many methods have been developed to remove the contaminant E-isomer. For example, the method disclosed in International Publication No. WO98/45299 comprises converting crude cefdinir into a salt of dicyclohexylamine, removing the impurity and reconvertng the purified salt to cefdinir. However, this multi-step method is inefficient and gives a low productivity.

US Patent No. 4,935,507 discloses a method of producing crystalline cefdinir, which comprises the steps of reacting amorphous cefdinir with an acid in a solvent and adding a non-polar solvent thereto to precipitate an acid-added salt of cefdinir, e.g., cefdinir.HCl, cefdinir.H₂SO₄ and cefdinir.CH₃SO₃H. However, the acid-added salt formed as an intermediate in this method is an amorphous bulky material which has poor stability and shows low purity.

Thus, there has continued to exist a need to develop an improved process for preparing a highly pure cefdinir.

Summary of the Invention

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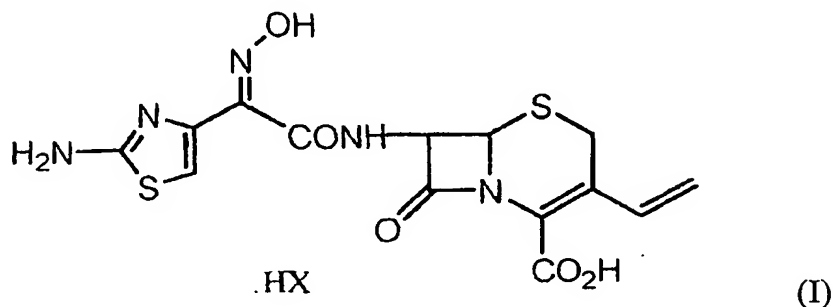
Accordingly, it is a primary object of the present invention to provide an efficient method of preparing high purity cefdinir.

It is another object of the present invention to provide a crystalline acid salt of cefdinir with high purity which can be advantageously used in the preparation of high purity cefdinir.

It is a further object of the present invention to provide a process for the

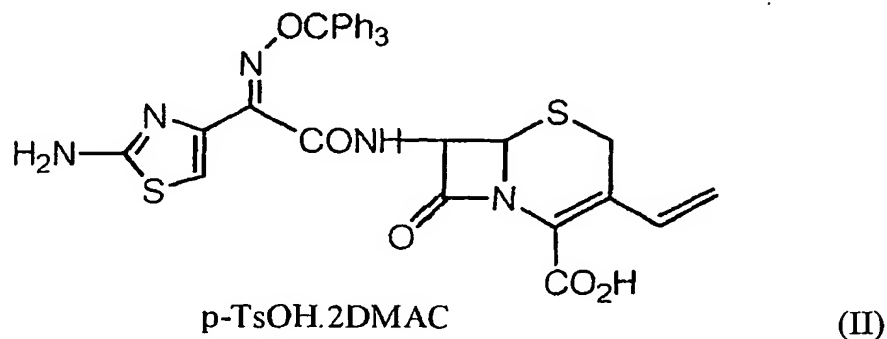
preparation of the crystalline acid salt of cefdinir.

In accordance with one aspect of the present invention, there is provided a crystalline acid salt of cefdinir of formula (I):



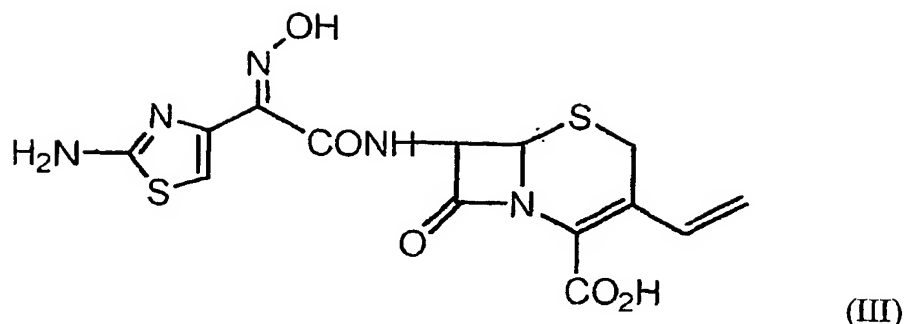
wherein HX is H_2SO_4 or $\text{CH}_3\text{SO}_3\text{H}$.

10 In accordance with another aspect of the present invention, there is provided a method of preparing a compound of formula (I) which comprises reacting a cefdinir intermediate of formula (II) with a formic acid-sulfuric acid mixture or a formic acid-methanesulfonic acid mixture in a solvent:



wherein Ph is phenyl,
p-TsOH is p-toluenesulfonic acid, and
DMAC is N,N-dimethylacetamide.

20 In accordance with a still another aspect of the present invention, there is provided a method of preparing cefdinir of formula (III) which comprises reacting the compound of formula (I) with a base in a solvent:



Brief Description of the Drawings

5 The above and other objects and features of the present invention will become apparent from the following description of the invention taken in conjunction with the following accompanying drawings, which respectively show:

10 Figures 1 and 3 : powder X-ray diffraction patterns of cefdinir.H₂SO₄ and cefdinir.CH₃SO₃H, respectively, prepared in accordance with the prior art ; and

 Figures 2 and 4 : powder X-ray diffraction patterns of cefdinir.H₂SO₄ and cefdinir.CH₃SO₃H, respectively, prepared in accordance with the inventive method.

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Detailed Description of the Invention

 The crystalline acid salt of cefdinir of formula (I) may be prepared by treating a cefdinir intermediate of formula (II) with a formic acid-sulfuric acid mixture or a formic acid-methanesulfonic acid mixture in a suitable solvent.

20 The cefdinir intermediate of formula (II) used in the present invention may be prepared using the reactions and techniques described in US Patent No. 6,093,814.

 The content of formic acid used in the present invention is 99 to 70 %, preferably 95 to 80 % and remainder is water. The amount of the formic acid used may range from 5 to 30 equivalents, preferably from 10 to 20 equivalents, based on the amount of the cefdinir intermediate of formula (II).

 Further, the amount of the sulfuric acid or methanesulfonic acid used in the inventive process may range from 2 to 5 equivalents, preferably from 2.5 to 3.5 equivalents, based on the amount of the cefdinir intermediate of formula (II).

30

Exemplary solvents which may be suitably used in the above reaction are any one selected from the group consisting of acetonitrile, diethyl ether, tetrahydrofuran, 1,4-dioxane, ethyl acetate, methylene chloride, chloroform, isopropanol, ethanol and a mixture thereof, wherein acetonitrile is preferred.

5 The amount of the solvent used may range from 2 to 20 volumes(ml/g), preferably from 4 to 10 volumes(ml/g) based on the amount of the cefdinir intermediate of formula (II).

The above reaction in accordance with the present invention may be performed at a temperature ranging from 5 to 40 °C, preferably from 10 to

10 30 °C, for a period ranging from 8 to 20 hours.

The acid salts of cefdinir prepared in accordance with the present invention are novel crystalline monosulfuric acid and monomethanesulfonic acid salt of cefdinir, unlike the amorphous acid salts disclosed in the prior art.

Further, highly pure cefdinir of formula (III) can be obtained easily by

15 simply treating the crystalline acid salt of cefdinir of formula (I) with a base in a suitable solvent.

Exemplary solvents which may be suitably used in the above reaction are any one selected from the group consisting of water, ethanol, methanol, acetonitrile, 1,4-dioxane, isopropanol, acetone, methylethylketone,

20 methylisobutylketone and a mixture thereof, wherein a mixture of water and ethanol is preferred. The amount of the solvent used may range from 5 to 30 volumes(ml/g), preferably from 10 to 20 volumes(ml/g) based on the amount of the acid salt of cefdinir of formula (I).

Exemplary bases which may be suitably used in the above reaction

25 include aqueous ammonia, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, sodium acetate, potassium acetate, sodium ethylhexanoate, triethylamine, diisopropylethylamine, dimethylethylamine, tributylamine, pyridine, dimethylbenzylamine, triethanolamine, dimethylaminopyridine and a mixture

30 thereof, wherein sodium acetate is preferred. The base may be used in an amount ranging from 1 to 3 equivalents based on the amount of the compound of formula (I) to adjust the pH at 1.5 to 3.5.

Acid addition salt of cefdinir in accordance with the inventive process is characteristically formed in the reaction solution while deprotecting a cefdinir

35 intermediate of formula (II). More characteristically, the inventive process described above gives a higher yield and a higher purity of crystalline acid salt of cefdinir as compared with any of the conventional methods. Specifically,

the purity is more than 99 % and contamination of E-isomer (anti-form) is surprisingly less than 0.1 %. Thus, according to the inventive process, acid addition salt of cefdinir is highly crystalline and shows high stability, from which highly pure cefdinir can be obtained in a high yield.

5

The following Reference Example and Examples are intended to further illustrate the present invention without limiting its scope; and the experimental methods used in the present invention can be practiced in accordance with the Reference Example and Examples given below, unless otherwise stated.

10 Further, percentages given below for solid in solid mixture, liquid in liquid, and solid in liquid are on the bases of wt/wt, vol/vol and wt/vol, respectively, unless specifically indicated otherwise.

15 Reference Example 1: Preparation of 7 β -[(Z)-2-(2-aminothiazol-4-yl)-2-trityloxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid-p-TsOH.2DMAC

20 8.0 g of 7-amino-3-vinyl-3-cephem-4-carboxylic acid and 21.5 g of (Z)-(2-aminothiazol-4-yl)-2-trityloxyiminoacetic acid 2-benzothiazolylthioester were suspended in 80 ml of N,N-dimethylacetamide and 16.8 ml of tri-n-butylamine was added thereto. Then, the mixture was stirred for 1 hour while maintaining the temperature at 15 to 20°C. 240 ml of diethyl ether was added thereto and stirred for 30 minutes, and then filtered through a cellite. Added to the filtrate was 20.2 g of p-toluenesulfonic acid.monohydrate dissolved in 40
25 ml of methanol and the resulting solution was stirred for 2 hours at room temperature. After 160 ml of diethyl ether was added thereto, the resulting solution was further stirred for 1 hour at room temperature, cooled to 0 to 5°C, stirred for 1 hour and filtered. The precipitate thus obtained was washed
30 50 ml of diethyl ether, and then dried to obtain 32.3 g(Yield: 93%) of the title compound as a pale yellow solid.

HPLC purity : 99.2%

35 H-NMR(δ , MeOH- d_4) : 2.08(6H,s, CH_3CO), 2.31(3H,s, CH_3Ph), 2.94(3H,s,-N- CH_3), 3.01(3H, s,-N- CH_3), 3.7(2H,brd s,C-2), 4.96(1H,s,C-6), 5.22~5.34(2H,m,- $CH=CH_2$), 5.67(1H,s,C-7), 6.67(1H,s,aminothiazol ring-H), 7.06~7.29(20H,m,- NH_2 , - $CH=CH_2$, Ph_3C -, CH_3Ph), 7.52(2H,d, 2, CH_3Ph)

Example 1: Preparation of 7 β -[(Z)-2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid.H₂SO₄

5 40g of 7 β -[(Z)-2-(2-aminothiazol-4-yl)-2-trityloxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid.p-TsOH.2DMAC obtained in Reference Example 1 was suspended in 200 ml of acetonitrile. 20 ml of 90% formic acid and 6.0 ml of 98% sulfuric acid were added thereto and then reacted for 20 hours while maintaining the temperature at 15 to 20 °C. The precipitate thus
10 obtained was filtered and washed sequentially with 100 ml of acetonitrile and 100 ml of diethyl ether, and then dried to obtain 18.2 g(Yield: 91%) of the title compound as a pale yellow crystalline solid.

HPLC purity : 99.9%

15 E – isomer : 0.08%

Melting point : 180 °C (decomposition)

IR(cm⁻¹,KBr) : 3391, 3225, 3116, 1774, 1651, 1526, 1164, 1042, 877, 672, 589, 570

20 H-NMR(δ ,DMSO-d₆) : 3.62, 3.85(2H,ABq,C-2), 5.24(1H,d,C-6), 5.35(1H,d,-CH=CH₂), 5.62(1H,d,-CH=CH₂), 5.78 ~ 5.83(1H,m,C-7), 6.88(1H,s, aminothiazol ring-H), 6.90 ~ 7.00(1 H,m,-CH=CH₂), 9.81(1H,d,-NH-)

25 The X-ray diffraction pattern in Fig. 2 shows that the cefdinir.H₂SO₄ thus obtained is highly crystalline, which should be compared with the broad peak pattern for the cefdinir sulfate prepared in accordance with the conventional method (Fig 1). The peaks observed in Fig. 2 are summarized in Table 1.

30

35

Table 1

2θ	d	I/I_0	2θ	d	I/I_0
8.4	10.5	100	20.3	4.4	73
9.4	9.4	21	21.2	4.2	39
11.8	7.5	28	23.0	3.9	38
14.1	6.3	61	23.8	3.7	80
17.0	5.2	30	25.2	3.5	48
18.6	4.8	95	27.4	3.3	38
19.0	4.7	55	28.7	3.1	36
19.6	4.5	32	30.0	3.0	30

d : lattice parameter; and

5 I/I_0 : relative peak intensity

Example 2: Preparation of 7β -[(Z)-2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid. $\text{CH}_3\text{SO}_3\text{H}$

10 100g of 7β -[(Z)-2-(2-aminothiazol-4-yl)-2-trityloxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid.p-TsOH.2DMAC obtained in Reference Example 1 was suspended in 200 ml of acetonitrile. 40 ml of 85% formic acid and 18.5 ml of methanesulfonic acid were added thereto, and then reacted for 20 hours while maintaining the temperature at 20 to 25 °C. The precipitate
15 thus obtained was filtered and washed sequentially with 100 ml of acetonitrile and 100 ml of diethylether, and then dried to obtain 43.9 g(Yield 88%) of the title compound as a pale yellow crystalline solid.

HPLC purity : 99.8%

20 E – isomer : 0.12%

Melting point : 210°C (decomposition)

IR(cm^{-1} ,KBr) : 3285, 3231, 1775, 1684, 1636, 1527, 1356, 1195, 1145, 1043, 782, 590

25 H-NMR(δ ,DMSO- d_6) : 2.37(3H,s, CH_3S),3.58, 3.82(2H,ABq,C-2), 5.21(1H,d,C-6), 5.32(1H,d,-CH=CH₂), 5.60(1H,d,-CH=CH₂), 5.75~5.80(1H,m,C-7), 6.85(1H,s, aminothiazol ring-H), 6.86~6.96(1 H,m,-CH=CH₂), 9.83(1H,d,-NH-)

The highly crystalline nature of the cefdinir. $\text{CH}_3\text{SO}_3\text{H}$ is verified by the powder X-ray diffraction pattern shown in Fig. 4. The cefdinir. $\text{CH}_3\text{SO}_3\text{H}$ prepared in accordance with the prior art method is amorphous as showed in Fig 3. The peaks observed in Fig. 4 are summarized in Table 2.

Table 2

2 θ	d	I/I ₀	2 θ	d	I/I ₀
6.1	14.4	44	21.8	4.1	100
11.8	7.5	38	22.0	4.0	90
13.3	6.7	28	22.6	3.9	30
16.5	5.4	30	23.7	3.8	27
17.0	5.2	21	24.3	3.7	22
19.0	4.7	26	24.9	3.6	52
19.7	4.5	38	25.5	3.5	17
20.6	4.3	17	31.1	2.9	17

10

Example 3: Preparation of 7 β -[(Z)-2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (cefdinir)

3.0g of 7 β -[(Z)-2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid. H_2SO_4 obtained in Example 1 was suspended in 30 ml of water and adjusted to pH 3.4 to 3.6 with 1.0 g of sodium bicarbonate. The resulting solution was stirred at a temperature ranging from 30 to 40 °C for 30 minutes, cooled to 0 to 5 °C, and then stirred for 30 minutes. The precipitate thus obtained was filtered and washed with 30 ml of distilled water, and then dried to obtain 1.40 g(Yield 87%) of the title compound as a pale yellow crystalline solid.

HPLC purity : 99.9%

E - isomer content : 0.06%

H-NMR(δ ,DMSO- d_6) : 3.57, 3.85(2H,ABq,C-2), 5.20(1H,d,C-6), 5.32(1H,d,-CH=CH₂), 5.61(1H,d,-CH=CH₂), 5.79~5.83(1H,m,C-7), 6.69(1H,s,aminothiozol ring-H), 6.89~6.98(1 H,m,-CH=CH₂), 7.14(2H, brd s,

-NH₂), 9.79(1H,d,-NH-).

Example 4: Preparation of 7β -[(Z)-2-(2-aminothiazol-4-yl)-2-hydroxyaminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (cefdinir)

5

5.0 g of 7β -[(Z)-2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid. CH₃SO₃H obtained in Example 2 was suspended in 50 ml of ethanol and adjusted to pH 3.4 to 3.6 by adding triethylamine thereto dropwise. The resulting solution was stirred at a temperature ranging from 30 to 35 °C for 30 minutes. The precipitate thus obtained was filtered, dispersed in a mixture of 30 ml of distilled water and 10 ml of ethanol, stirred at a temperature ranging from 30 to 35 °C for 30 minutes, filtered, washed with 20 ml of distilled water, and then dried to obtain 3.31 g (Yield: 82%) of the title compound as a pale yellow crystalline solid.

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HPLC purity : 99.8%

E - isomer content : 0.08%

H-NMR data of this product were identical with those of the compound prepared in Example 3.

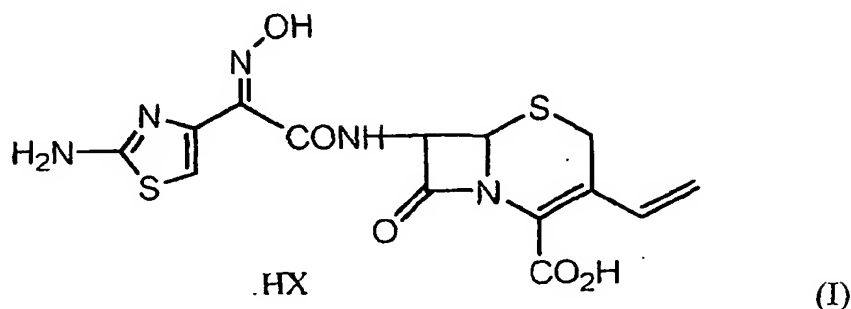
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While the invention has been described with respect to the above specific embodiments, it should be recognized that various modifications and changes may be made to the invention by those skilled in the art which also fall within the scope of the invention as defined by the appended claims.

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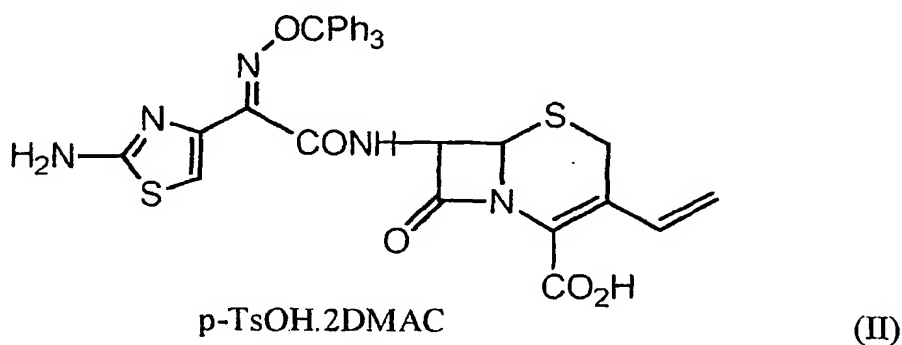
What is claimed is :

1. A crystalline acid salt of cefdinir of formula (I):



wherein HX is H_2SO_4 or $\text{CH}_3\text{SO}_3\text{H}$.

2. A method of preparing the crystalline acid salt of cefdinir of formula (I) recited in claim 1 which comprises reacting a cefdinir intermediate of formula (II) with a formic acid-sulfuric acid mixture or a formic acid-methanesulfonic acid mixture in a solvent:



wherein Ph is phenyl,
p-TsOH is p-toluenesulfonic acid, and
DMAC is N,N-dimethylacetamide.

3. The method of claim 2, wherein the formic acid is an aqueous solution having a formic acid content of 99 to 70 %.

4. The method of claim 2, wherein the formic acid is used in an amount ranging from 5 to 30 equivalents based on the amount of the cefdinir

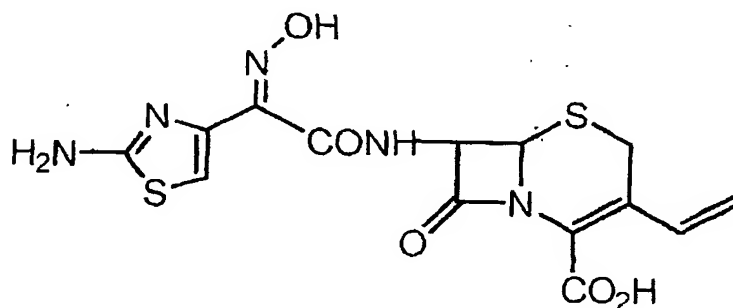
intermediate of formula (II).

5. The method of claim 2, wherein sulfuric acid or methanesulfonic acid is used in an amount ranging from 2 to 5 equivalents based on the amount of the cefdinir intermediate of formula (II).

6. The method of claim 2, wherein the solvent is selected from the group consisting of acetonitrile, diethyl ether, tetrahydrofuran, 1,4-dioxane, ethyl acetate, methylene chloride, chloroform, isopropanol, ethanol and a mixture thereof.

7. The method of claim 2, wherein the solvent is acetonitrile.

8. A method of preparing cefdinir of formula (III) which comprises reacting the crystalline acid salt of cefdinir of formula (I) with a base in a solvent:

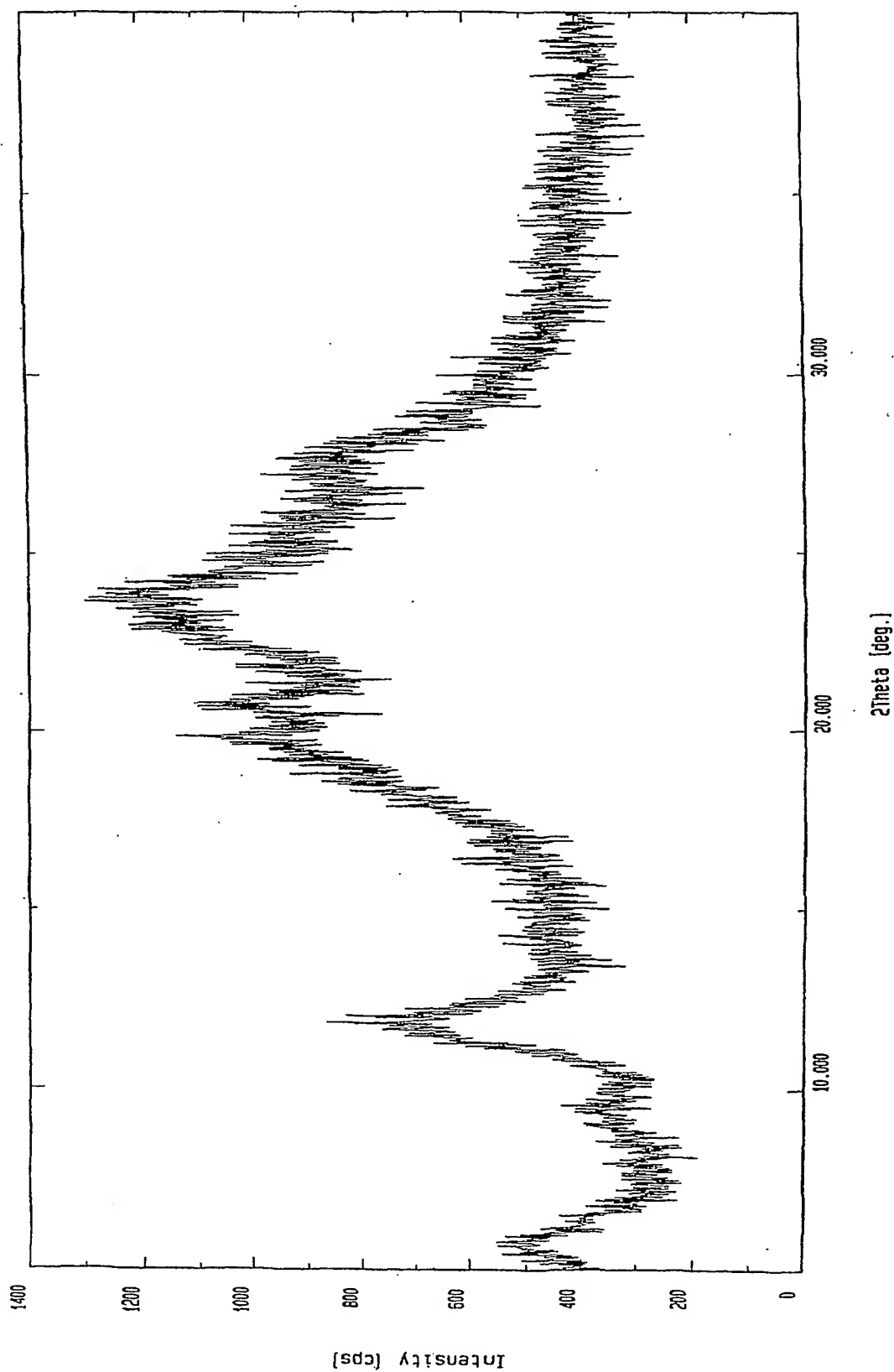


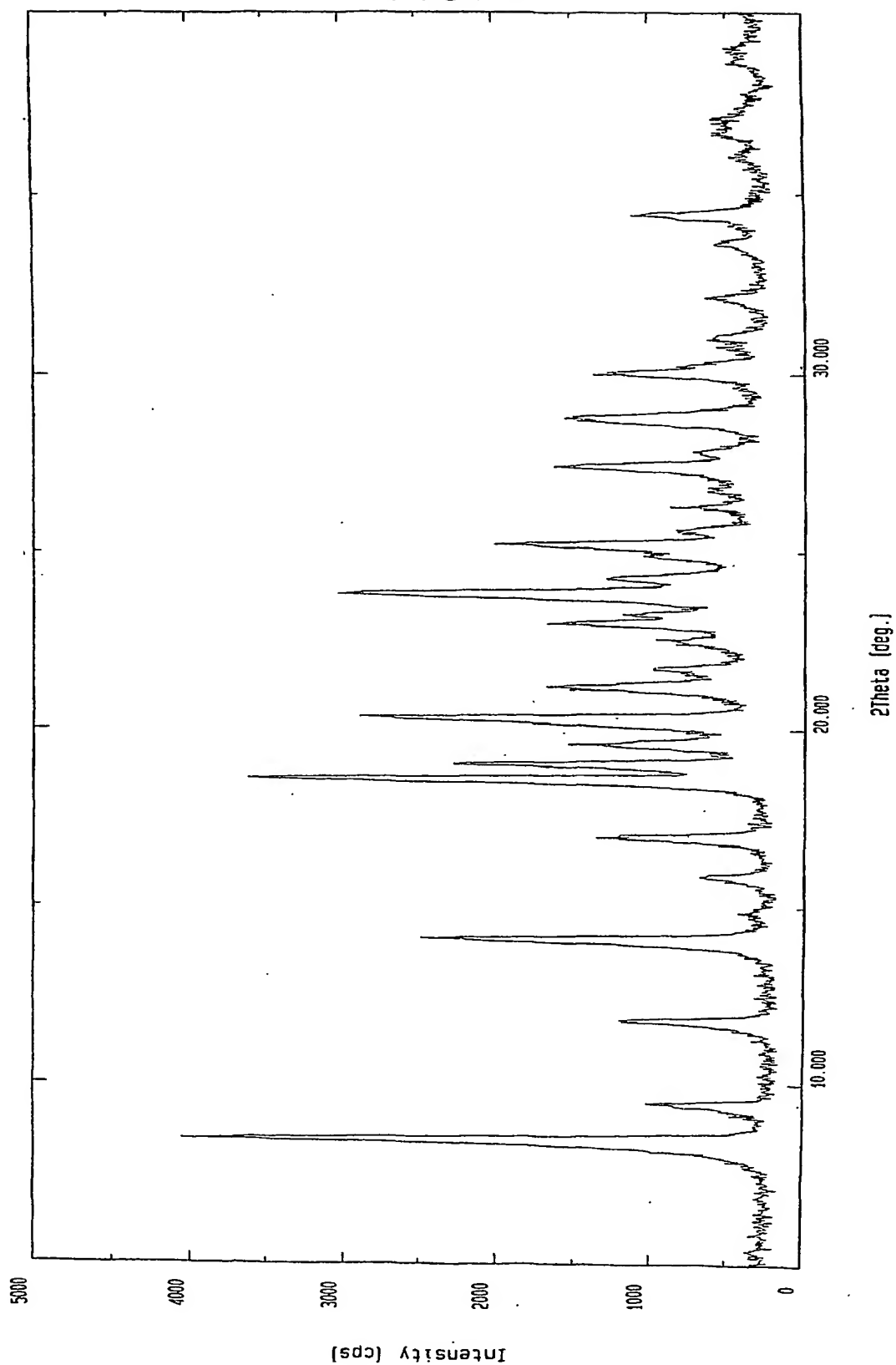
(III)

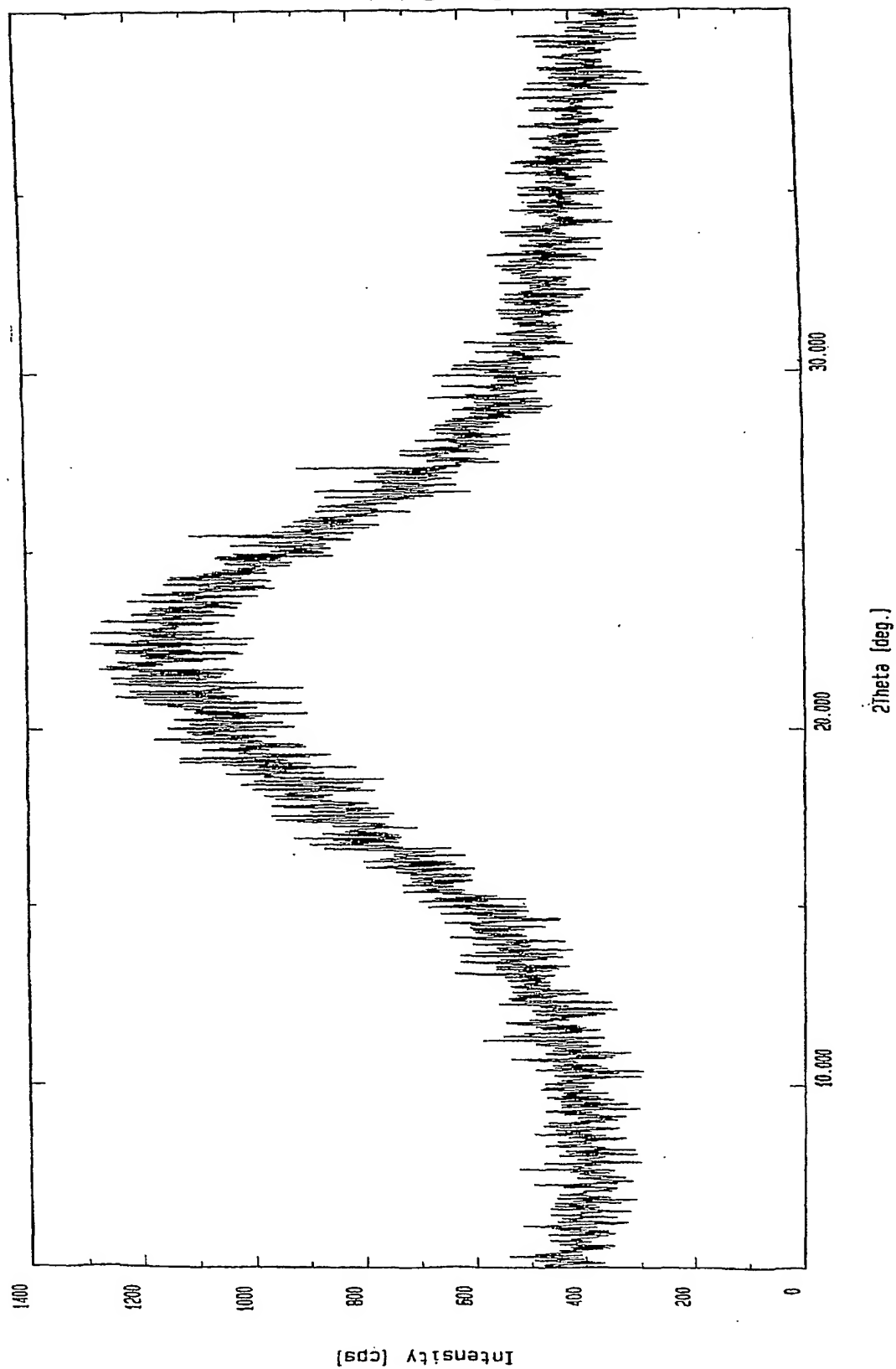
9. The method of claim 8, wherein the solvent is selected from the group consisting of water, ethanol, methanol, acetonitrile, 1,4-dioxane, isopropanol, acetone, methylethylketone, mehtylisobuthylketone and a mixture thereof.

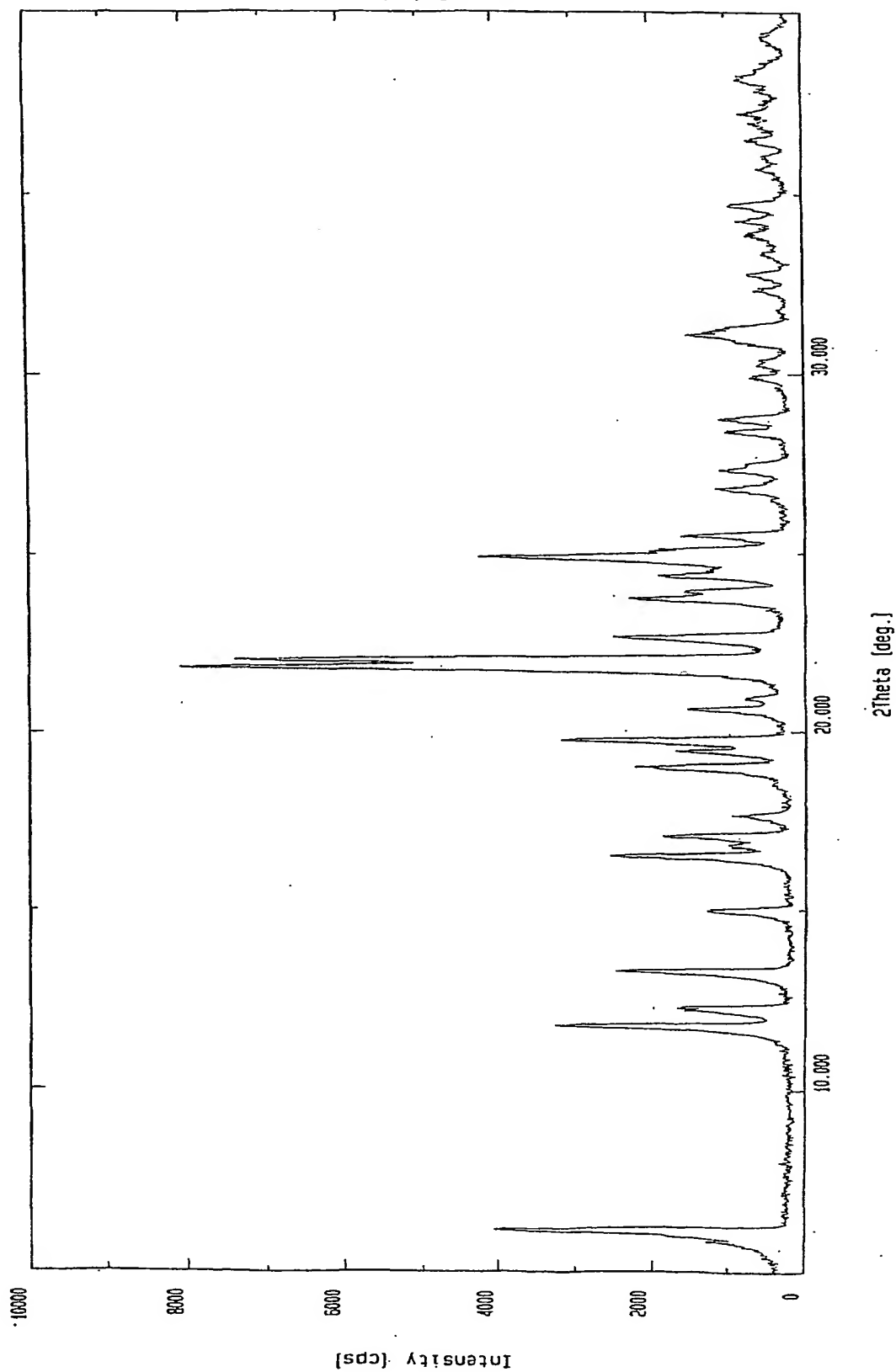
10. The method of claim 8, wherein the base is selected from the group consisting of aqueous ammonia, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, sodium acetate, potassium acetate, sodium ethylhexanoate, triethylamine, diisopropylethylamine, dimethylethylamine, tributylamine, pyridine, dimethylbenzylamine, triethanolamine, dimethylaminopyridine and a mixture thereof

11. The method of claim 10, wherein the base is sodium acetate.

1/4
FIG. 1



2/4
FIG. 2

3/4
FIG. 3

4/4
FIG. 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR02/01064

A. CLASSIFICATION OF SUBJECT MATTER IPC7 C07D 501/22 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC7 C07D Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Korean Patents and applications for inventions since 1975 Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) CAPLUS(STN)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim
A	WO 98/45299 A1(BIOCHEMIE GESELLSCHAFT MBH.) 15 OCTOBER 1998, SEE THE WHOLE DOCUMENT	1-2, 8
A	WO 97/24358 A1(HANMI PHARMACEUTICAL CO., LTD.) 10 JULY 1997, SEE ABSTRACT, EXAMPLES AND CLAIMS	1 - 2, 8
A	SAKANE, KAZUO; KAWABATA, KOHJI 'Research and development of new oral cepheims, cefixime and cefdinir', Yakugaku Zasshi (1993), 113(9), p605-26, SEE THE WHOLE DOCUMENT	8
A	JP 02-790 A2(FUJISAWA PHARMACEUTICAL CO., LTD.,) 5 JANUARY 1990, SEE THE WHOLE DOCUMENT	8
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.		
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Date of the actual completion of the international search 30 SEPTEMBER 2002 (30.09.2002)		Date of mailing of the international search report 30 SEPTEMBER 2002 (30.09.2002)
Name and mailing address of the ISA/KR  Korean Intellectual Property Office 920 Dunsan-dong, Seo-gu, Daejeon 302-701, Republic of Korea Facsimile No. 82-42-472-7140		Authorized officer WON, Ho Joon Telephone No. 82-42-481-5605 

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR02/01064

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 98/45299 A1	15. 10. 1998	AT 9700570 A	15.11.1998
		AU 9874288 A1	30. 10. 1998
		EP 973779 A1	26. 01. 2000
		JP 2000-514833 T2	07. 11. 2000
		US 6350869 B1	26. 02. 2000
WO 97/24358 A1	10. 07. 1997	EP 874853 A1	04. 11. 1998
		JP 2000-502700 T2	07. 03. 2000
		US 6093814 A	25. 07. 2000
JP 02-790 A2	05. 01. 1990	ES 2013828 A6	01. 06. 1990

Form PCT/ISA/210 (patent family annex) (July 1998)

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